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Research Paper

Enteric Coated Magnetic HPMC Capsules Evaluated in Human Gastrointestinal Tract by AC Biosusceptometry

Luciana A. Corá,[1] Fernando G. Romeiro,[2] Fabiano C. Paixão,[1] Madileine F. Américo,[3] Ricardo B. Oliveira,[3] Oswaldo Baffa,[4] and José Ricardo A. Miranda[1,5,6]

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Purpose. To employ the AC Biosusceptometry (ACB) technique to evaluate *in vitro* and *in vivo* characteristics of enteric coated magnetic hydroxypropyl methylcellulose (HPMC) capsules and to image the disintegration process.
Materials and Methods. HPMC capsules filled with ferrite ($MnFe_2O_4$) and coated with Eudragit® were evaluated using USP XXII method and administered to fasted volunteers. Single and multisensor ACB systems were used to characterize the gastrointestinal (GI) motility and to determine gastric residence time (GRT), small intestinal transit time (SITT) and orocaecal transit time (OCTT). Mean disintegration time (t_{50}) was quantified from 50% increase of pixels in the imaging area.
Results. *In vitro* and *in vivo* performance of the magnetic HPMC capsules as well as the disintegration process were monitored using ACB systems. The mean disintegration time (t_{50}) calculated for *in vitro* was 25 ± 5 min and for *in vivo* was 13 ± 5 min. *In vivo* also were determined mean values for GRT (55 ± 19 min), SITT (185 ± 82 min) and OCTT (240 ± 88 min).
Conclusions. AC Biosusceptometry is a non-invasive technique originally proposed to monitoring pharmaceutical dosage forms orally administered and to image the disintegration process.

KEY WORDS: biosusceptometry; colonic drug delivery; gastrointestinal motility; HPMC capsules; magnetic images.

INTRODUCTION

Colon-specific delivery has renewed interest in the development of therapeutic agents for treating colonic diseases because it maximizes its effectiveness and provides systemic absorption of drugs susceptible to enzymatic digestion in upper gastrointestinal (GI) tract (1,2).

Many colon-specific dosage forms have been developed for oral or rectal administration. However, oral route is preferred since rectal dosage forms have limited action and variability in distribution of the drug (2).

A common strategy to achieve colon specificity is the coating of oral solid dosage forms employing polymers with a pH-dependent solubility. The majority of enteric and colon delivery systems are based on coated tablets or conventional hard gelatin capsules (3). Nevertheless, capsules made from hydroxypropyl methylcellulose (HPMC) have been successfully manufactured as an alternative to gelatin (4). HPMC capsules have several technical advantages over gelatin capsules including a more irregular surface that provides a strongly adhesion and an excellent compatibility with the polymer (3,4).

Coated dosage forms designed for oral colon-specific drug delivery must overcome several physiological barriers that include motility patterns, GI transit and difference between the luminal pH (5). Moreover, the disintegration of the solid dosage form must be taken into consideration since this process provides the drug release for the absorption (6,7). For this reason *in vitro* tests are needed although the results are not fully comparable to the physiological conditions (8). More reliable data are obtained when human studies are carried out, since the bioavailability of drugs from colonic dosage forms is dependent on gastric emptying, small intestinal transit time and drug release profile (9).

Imaging techniques play an important role for monitoring of pharmaceutical dosage forms in human GI tract (10). The γ-scintigraphy is the method of choice for this purpose, despite exposure of the patient to ionizing radiation and the complicated and expensive preparation of radiopharmaceuticals (11).

[1] Departamento de Física e Biofísica, IBB, Universidade Estadual Paulista—UNESP, Distrito Rubião Jr, s/n, CXP 510, CEP 18618-000, Botucatu, São Paulo, Brazil.
[2] Departamento de Clínica Médica, FM, Universidade Estadual Paulista—UNESP, Botucatu, São Paulo, Brazil.
[3] Departamento de Clínica Médica, FMRP, Universidade de São Paulo—USP, Ribeirão Preto, São Paulo, Brazil.
[4] Departamento de Física e Matemática, FFCLRP, Universidade de São Paulo–USP, Ribeirão Preto, São Paulo, Brazil.
[5] Distrito Rubião Jr, s/n, CXP 510, CEP 18618-000, Botucatu, São Paulo, Brazil.
[6] To whom correspondence should be addressed. (e-mail:jmiranda@ibb.unesp.br)

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On the other hand, radiation-free modalities introduced a new perspective for the *in vivo* investigation of drug delivery. Magnetic Resonance Imaging (MRI) has been employed to monitor solid pharmaceutical forms in animals and healthy subjects (12–14). Regardless of widespread use in clinical and inherent advantages, MRI has limited application in pharmaceutical research due to the high cost, the positioning of the subject during the exposure and the contrast agents do not represent an ideal drug model.

Biomagnetic methods are feasible alternative in clinical, physiological and pharmaceutical research and the multichannel SQUID (*Superconducting Quantum Interference Device*) devices are employed for the measurement of the magnetic field, after ingestion of a magnetically marked dosage form (15). This system is able to detect the extremely weak biomagnetic fields generally in a magnetically shielded environment. However, SQUID has an expensive operational cost, which limits its use in a wide scale.

Alternating Current Biosusceptometry (ACB) has been introduced as a valuable tool in gastroenterology (16) and pharmaceutical research (17). ACB uses induction coils for recording the magnetic flux variation obtained from the response of a magnetic material ingested (18). The ACB showed accuracy to evaluate physiologically different parameters of GI tract (16,19–22) as well as to obtain the magnetic images *in vitro* (23).

A multisensor ACB system was implemented to characterize the disintegration process of tablets *in vitro* and in the human stomach, through the acquisition of magnetic signals (17). In addition, this system was also employed to monitor magnetic tablets in GI tract and to image the disintegration process, introducing a novel technique in imaging of the biological systems (18,24,25).

Following these initial proposals, the aim of this work was to employ the single and multisensor ACB systems to determine the gastrointestinal transit time of enteric coated magnetic HPMC capsules and to image the disintegration process of these formulations in human ileocolonic region.

METHODS AND MATERIALS

Fundamentals

The single sensor ACB has two pairs of coils (ϕ = 3.0 cm) separated by a fixed distance (baseline), where each pair of coils are composed of an excitation coil (external) and a detection coil (internal), in the first-order gradiometric configuration (Fig. 1). This system working as a double magnetic flux transformer with an air nucleus, in which the pair (excitation/detection), located more distant from magnetic material (ferrite), acts as reference. Due to this configuration, when no magnetic material is near to the measurement system, the output signal is minimized. When there is an approximation of a magnetic mass, an unbalancing in the magnetic flux of the gradiometric system occurs, and the magnetic material is monitored (18,22,25).

The multisensor ACB has only a pair of excitation coil (ϕ = 11 cm) and seven pairs of detection coils (ϕ = 2.9 cm), coaxially arranged (Fig. 2). This system is fixed in a vertical support to be positioned on the abdominal surface and to acquire the magnetic signals at different points (17,18,24,25).

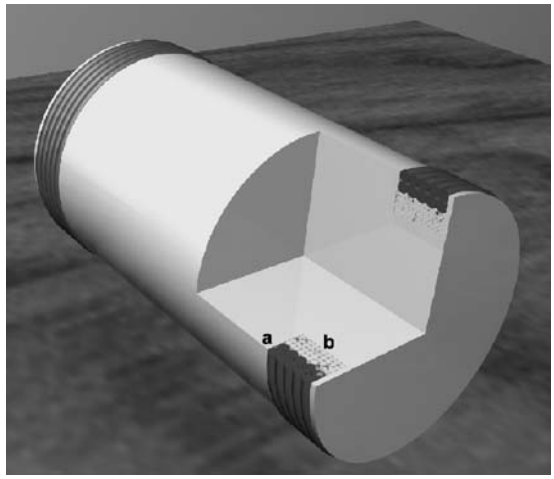

Fig. 1. Single sensor AC Biosusceptometer. (a) Excitation coil and (b) detection coil in the first-order gradiometric configuration.

The magnetic signals are acquired through "lock-in" amplifiers (Stanford Research Systems) digitalized by A/D board of 16 bits (PCI-MIO-16XE-10, National Instruments Inc.) and stored in a microcomputer.

Capsule Preparation

Size 00 capsules made from hydroxypropyl methylcellulose (Vcaps®, Capsugel Division of Pfizer Inc.) without colouring agent were filled with 1.20 g of ferrite ($MnFe_2O_4$-Ferroxcube, USA) into which had been mixed 0.30 g of sodium starch glycolate—Explotab® (Penwest, USA).

Ferrite is a ferromagnetic material with general composition $MeFe_2O_4$, where Me represents a divalent transition metal such as manganese (Mn). Ferrite was described as a contrast material or magnetic medicinal preparations (26,27). This material presents good mixing with the GI secretions, absence of toxicity, and lack effects on the digestive tract.

To provide a more objective chemical characterization for this material, the concentrations of iron ions in the dissolution medium were prepared according to USP XXII method (pH 1.2, pH 6.0 and pH 7.4) and were determined by FAAS (Flame Absorption Atomic Spectrometry) using Spectrophotometer SHIMADZU AA-6800. Standard solutions contained 0.50, 1.00, 2.00, 4.00 and 5.00 mg l^{-1} of Fe(III) ions in HCl 0.01 mol l^{-1} medium and were used in the calibration of spectrometer (according to the manufactures standard guidelines). No measured iron ion was detected in the samples collected at 0(control), 6, 12, 24 and 48 h, suggesting that the ferrite ($MnFe_2O_4$) is a stable molecule and is not absorbed by GI mucosa.

Commercially available system for colon specific drug delivery was used in this study. Eudragit® S 100 (Röhm, Pharma Polymers) is a methacrylic acid methylmethacrylate co-polymer, soluble above pH 7, making it particularly suitable for delivery into the colon (28).

Excipients used for the coating dispersions were triethyl citrate (Citroflex® 2 -Morflex Inc., USA) as a plasticizer, magnesium stearate as a lubricant, titanium dioxide employed as a pigment, Polysorbate 80 as an emulsifier and glycerol monostearate (Imwitor® 900 K Sasol, German) as a

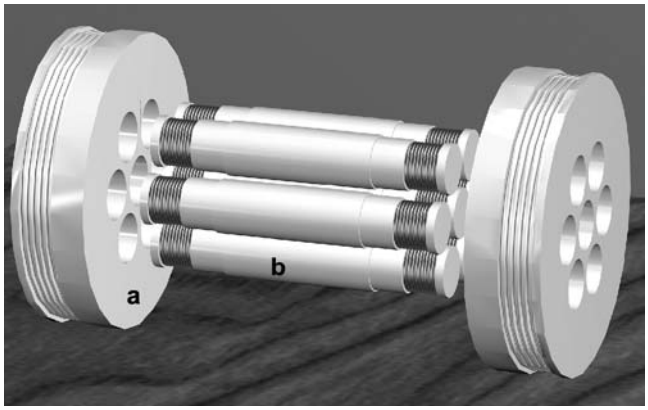

Fig. 2. Multisensor AC Biousceptometer system. (a) Pair of excitation coils and (b) seven pairs of detection coils coaxially arranged with a hexagonal symmetry.

glidant. Capsules were sealed before coating. The polymer dispersion was prepared according to manufacturer's technical information (29) and sprayed at temperatures of 25 to 27°C.

In-vitro Test

In order to simulate the pH changes along the gastrointestinal tract, three dissolution media (at 37 ± 0.5°C, volume 500 ml), prepared according to the USP XXII method, with pH 1.2, pH 6.0, and pH 7.4 were sequentially used. The magnetic formulations was first placed in a pH 1.2 medium for 2 h and after that in pH 6.0 dissolution medium. After 3 h, the formulation was placed in a square glass vessel containing the pH 7.4 dissolution medium that was positioned in front of the multisensor ACB system.

A digital camera was used to obtain images of the enteric coated magnetic HPMC capsule in the solution. When the formulation was introduced in the last dissolution medium video and magnetic signals were acquired simultaneously until complete ferrite release in the solution. *In vitro* disintegration process analysis was accomplished through the magnetic images obtained from the signals, as demonstrated in our previous study (24).

Subjects and Study Protocol

GI performance of enteric coated HPMC magnetic capsules was evaluated in ten healthy volunteers, both genders (age: 20–32 years; BMI: 20.11 ± 0.6 kgm^{-2}). All volunteers had no history of gastrointestinal symptoms or abdominal surgery. Written informed consent of participation in the studies had been obtained. The *in vivo* investigation was approved by the Ethic Committee in Research of the Medical School—Universidade Estadual Paulista (UNESP), in accordance with the Declaration of Helsinki, promulgated in 1964.

The enteric coated magnetic HPMC capsules were administered with the volunteers in an upright position in front of the multisensor ACB system. After an overnight fast, all subjects swallowed a capsule with 200 ml of water and the magnetic signals were recorded during 20 min. The lower tip of the sternum and the umbilicus were the anatomic references (Fig. 3a).

After that, a mapping from abdominal surface was carried out every 10 min employing the single-sensor ACB. This procedure aimed to locate the magnetic formulation to determine the Gastric Residence Time (GRT), the Small Intestinal Transit Time (SITT) and the Orocaecal Transit Time (OCTT). Eating or drinking was allowed after gastric emptying of the capsule. The subjects remained moderately active during the study period.

An initial square matrix (9×9), corresponding to an area of 12×12 cm, was drawn in ileocolonic region of the volunteers. The McBurney's point and iliac right crest were the anatomic references (Fig. 3b). With the arrival of enteric coated magnetic HPMC capsule in ileocolonic region, the single-sensor ACB was used to scan this delimited area. Scanning at least for 2 min and was performed at approximately 10 min intervals until 120 min post-ileocolonic arrival.

Magnetic Data Analysis

The performance of HPMC magnetic capsules along the GI tract was monitored using the single and multisensor

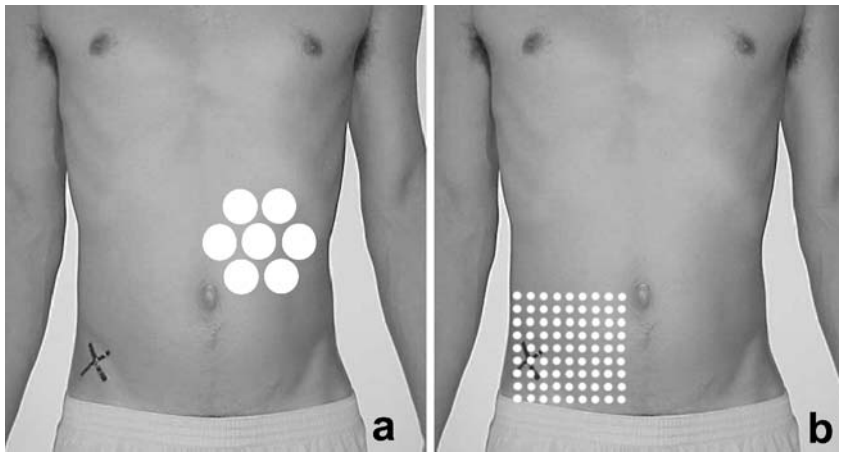

Fig. 3. (a) Positioning of the multisensor AC Biosusceptometer system on the abdominal surface. (b) Square matrix (9×9) draws on the ileocolonic region. The xiphoid process and the McBurney's point were the external anatomic references, respectively.

ACB systems. Initially, the magnetic signals were recorded from multisensor ACB with acquisition frequency of 10 Hz/channel and stored in ASCII format. The signal processing included bi-directional Butterworth low-pass filter with cutoff frequency of 0.2 Hz and Fast Fourier Transform (FFT) and allowed to characterize the gastric activity contraction (GAC) in the interdigestive period.

The Gastric Residence Time (GRT) was defined as the time interval between the arrival of the enteric coated magnetic HPMC capsule in the stomach and its gastric emptying. The Orocaecal Transit Time (OCTT) was calculated by determining the time between the intake of capsule and the location in the ileocolonic region. The Small Intestinal Transit Time (SITT) was obtained by subtracting the GRT from the OCTT.

The square matrixes (9×9) were interpolated (256×256) by the *spline* method and appropriate routines to obtain the degraded images of the enteric coated magnetic HPMC capsules *in vivo* were applied (25). Further image processing for quantification included: background subtraction, brightness and contrast adjustment and segmentation. The segmentation was used to quantify the spreading of the magnetic material and the velocity of disintegration (24). All the routines were implemented in MatLab® (Mathworks, Inc.).

The disintegration process for in vitro and in vitro measurements was characterized by the transition of a magnetic marker—MM (non-disintegrated capsule) to a magnetic tracer—MT (disintegrated capsule). In the magnetic images, the MM was clearly delineated and the MT showed the spreading of the magnetic material in the ileocolonic region. Disintegration process was calculated as the mean time disintegration (t_{50}) after reaching the ileocolonic region, and was obtained from the 50% increase of pixels in the imaging area (24,25).

RESULTS

Figure 4(a) illustrates a series of photographs of an enteric coated magnetic HPMC capsule in the phosphate buffer dissolution medium (pH 7.4). Instant t_1 represents 10 min of measurement and there was no occurrence of ferrite release. When the coating layer is reduced, the disintegration process (instant t_2) initiates and it is intensified due to the action of the excipients that promotes the spreading of the magnetic material in the glass vessel (instant t_3). The segmented area outlined in the photographs was used to calculate the mean time disintegration (t_{50}) from the 50% increase of pixels in the imaging area (Fig. 4b).

For the same instants shown in the photographs, the magnetic images were obtained from a capsule in dissolution medium and showed the disintegration process (Fig. 4c). In the instant t_1 the capsule can be observed as a MM. The onset of the disintegration process occurred in the instant t_2, with a gradual increase of the imaging area due to the spreading of the magnetic material (instant t_3). Fig. 4(d) shows the number of pixels contained inside a delineated area (spreading of the magnetic material) and its time variation ('velocity of disintegration'). The mean disintegration time (t_{50}) for *in vitro* measurements was 25 ± 5 (mean ± SD) min.

Gastric activity contraction (GAC) was recorded in real-time by the multisensor ACB, concomitantly to the ingestion of the HPMC capsule is showed in Fig. 5a. The variation of intensity and the basal level of the magnetic signals acquired by the sensors located more distally showed that the enteric

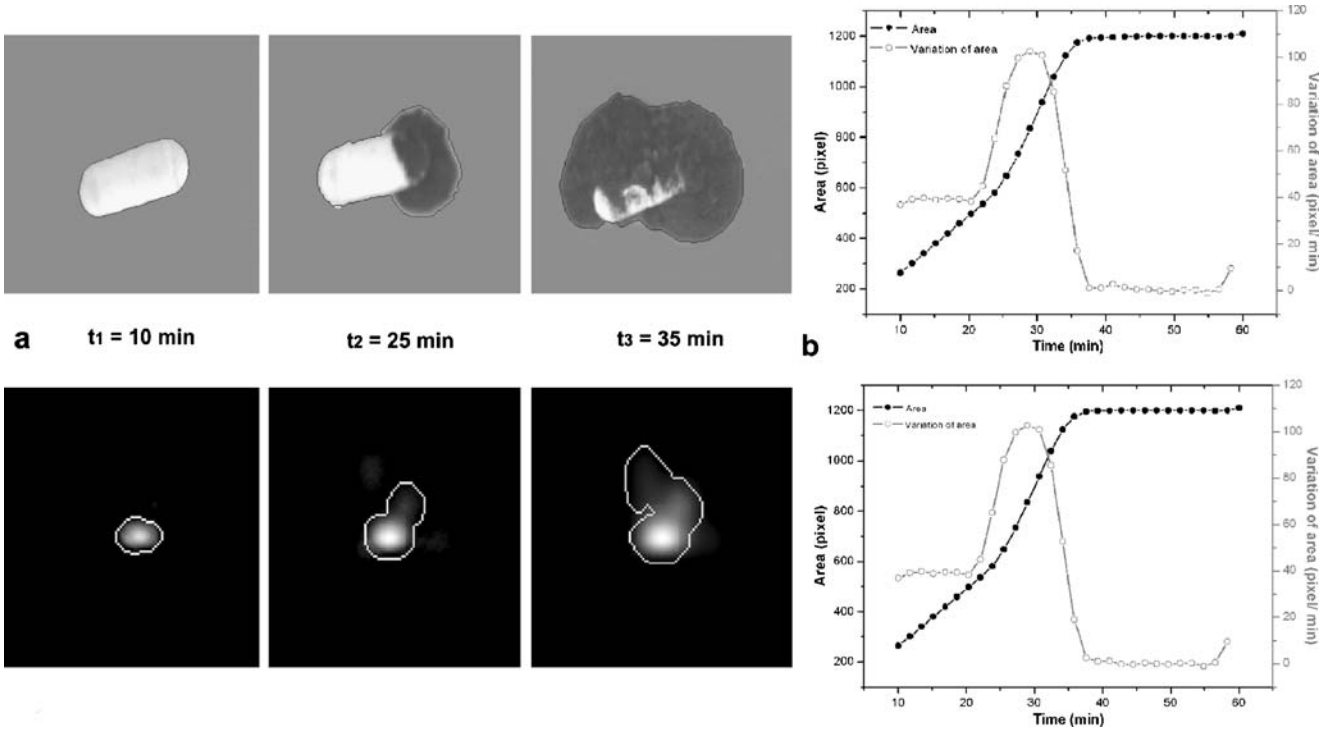

Fig. 4. *In vitro* characterization of an enteric coated magnetic HPMC capsule. (a) Photographs and corresponding magnetic images of the disintegration process of a capsule in the phosphate buffer. Mean disintegration time (t_{50}) occurred in the instant t_2. (b) Spreading of the magnetic material and the time variation of the number of pixels contained inside a delineated area showing the velocity of the disintegration.

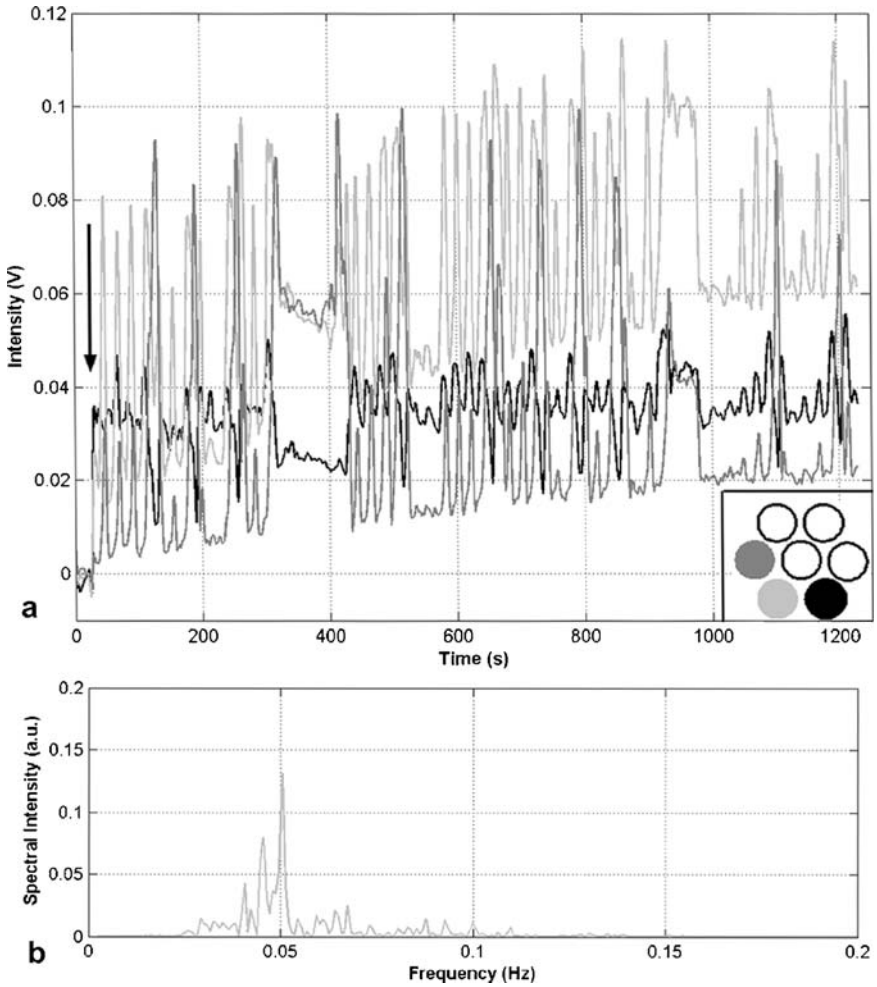

Fig. 5. Magnetic signals recorded concomitantly to the ingestion of the enteric coated HPMC capsule. (a) Intense contractile waves of the gastric activity recorded by the sensors located distally. (b) FFT showing the frequency peak of 0.05 Hz (3 cycles/minute).

coated magnetic HPMC capsule arrived on distal stomach (arrow).Typical frequency pattern around three cycles *per* minute (0.05 Hz) could be observed (Fig. 5b).

Table I. Gastrointestinal Transit Time and Mean Disintegration Time (t_{50}) for Magnetic Enteric Coated Magnetic HPMC Capsules

	Time (min)			
Volunteer	GRT	SITT	OCTT	t_{50}
1	60	190	250	10
2	40	190	230	10
3	40	90	130	20
4	50	380	430	10
5	50	150	200	10
6	80	140	220	10
7	60	210	270	10
8	70	230	300	20
9	20	100	120	20
10	80	170	250	10
X	55	185	240	13
SD	19	82	88	5
CV (%)	35	45	36	38

X Mean, *SD* standard deviation, *CV (%)* coefficient of variation.

The Gastric Residence Time (GRT) ranged from 20 to 80 min (mean 55 ± 19). Small Intestinal Transit Time (SITT) ranged from 90 to 380 min (mean 185 ± 82 min). Orocaecal Transit Time (OCTT) ranged from 120 to 430 min (mean 240 ± 88 min) (Table I).

Magnetic images of the disintegration process of magnetic HPMC capsules in the ileocolonic region for two volunteers are illustrated in Fig. 6a. The external anatomic references were delineated according to the positioning of the square matrix drawn on the abdominal surface (Fig. 3b). In instant t_1, the ileocolonic arrival of the HPMC capsule can be observed. The onset of disintegration occurred in the instant t_2. After t_3, a gradual increase in the imaging area can be verified, characterizing the spreading of the magnetic material within the organ.

The release of the magnetic material filled in the capsule occurred in the initial instants from the ileocolonic arrival. The number of pixels interpolated contained inside a segmented area and its time variation ("velocity of disintegration") is shown in Fig. 6b. After the onset of disintegration, the spreading of the magnetic material was relatively constant and significant variation in the image area was not observed. The *mean disintegration time* (t_{50}) was 13 ± 5 (mean ± SD) min.

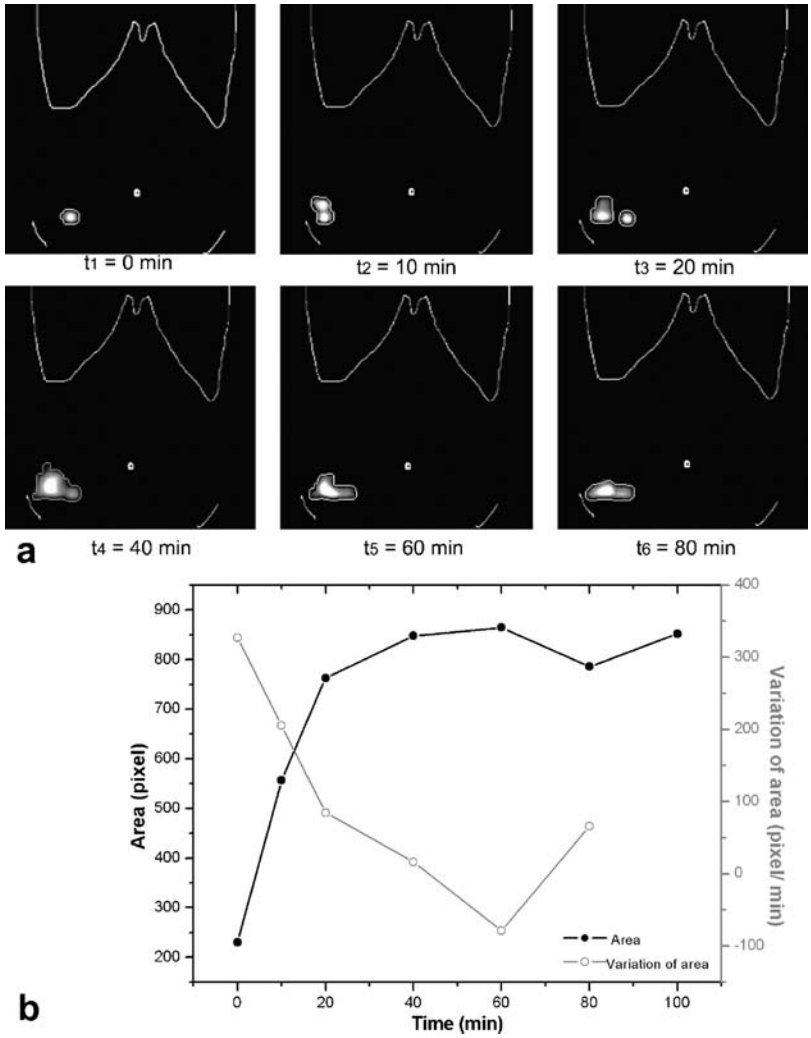

Fig. 6. (a) Magnetic images of the disintegration process of an enteric coated HPMC capsule in the ileocolonic region. The instant t_1 shows the arrival of the capsule; from t_2 occurred a gradual increase in the image area that characterized the spreading of the magnetic material. (b) Spreading of the magnetic material in number of pixels in the segmented area showing the velocity of the disintegration process.

DISCUSSION AND CONCLUSION

An ideal technique to provide more reliable data about pharmaceutical drug product performance in humans should be harmless, noninvasive and have low cost. Thus, AC Biosusceptometry has gained importance in the pharmaceutical research for evaluating successful magnetic solid dosage forms in human GI tract (17,18,25).

A variety of coated forms have not been developed with significant therapeutic advantages for the local treatment of colonic diseases (2,31). The use of coated dosage forms for oral colon specific drug delivery, allowing to develop enteric coated of HPMC capsules that appears as an industrially viable process, resulting from improved coating technologies and flexibility in their design (3,38).

The polymers used for colon targeting exploit the generally accepted fact that pH of the human GI tract increases progressively from the stomach at the distal ileum (30).Therefore, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral to slightly alkaline pH of the terminal ileum or at the ileocecal junction (5,28).

In order to characterize the disintegration profiles from the magnetic HPMC capsules coated with Eudragit® S 100 an *in vitro* study was performed. None of the capsules released ferrite in acid medium or at pH 6.0, showing integrity of the coating layer under simulated gastric and small intestine medium.

Aiming to compare quantitatively the disintegration profiles, photographs and the corresponding magnetic images were analyzed (Fig. 4). The capsule was suitable to release rapidly the magnetic material at pH 7.4 as shown in the instant t_2. Once initiated, the disintegration promotes the dispersion of the ferrite continuously (instant t_3).

Magnetic images are different from the photographs since the field-of-views are not the same because they were obtained at distinct angles and distances. Despite this, employing ACB

it was possible to characterize the disintegration process by comparing the similar profiles with those obtained by photographs (Fig. 4). *In vitro* disintegration of the capsules suggests good performance of ACB and ferrite release only in the distal ileum or the proximal colon.

Although disintegration process can be studied *in vitro*, the interaction between physiological parameters and the solid dosage forms affect drug delivery profile and the reproducibility of drug release (8). If the intended site of drug release is the colon, it must be taken into consideration the prandial state and gastric emptying of dosage forms.

ACB system was able to record in real-time the gastric motility during the interdigestive period (Fig. 5), characterized by a cyclical motor pattern so-called myoelectric migrating complex (MMC) (32). Phase III contractions promote the emptying of indigestible materials, including solid pharmaceutical forms (33,34). In the presented study, all volunteers fasted prior to the administration of the magnetic formulation, allowing inferring that the capsules had been emptied from stomach during this period of activity.

Gastric residence time (GRT) for enteric coated magnetic HPMC capsules was obtained from the arrival in the stomach until its emptying (Table I). The mean GRT was 55 min showing an important intersubject variation despite of experimental protocol had been designed to minimize the influence of any external factor in the gastric emptying of the magnetic formulation.

The results from our investigation (Table I) showed that the SITT presented a significant intersubjects variation (mean 185 ± 82 min), however are within the normal ranges obtained in previous studies (33,37). As reported by other studies, it is generally accepted that small intestinal transit time (SITT) is not affected by the digestive state or by the nature of the pharmaceutical form (33,35,36).

Orocaecal transit time (OCTT) occurred on average at 240 ± 88 min (Table I). The variation observed can be attributed to the GRT and SITT, since these parameters showed significant intersubject differences as discussed earlier. Not surprisingly, GI transit for enteric coated magnetic tablets (25) compared with magnetic HPMC capsules was not significantly different for the GRT and SITT.

Mean disintegration time for magnetic capsules occurred in a short time interval (mean 13 ± 5 min), when compared with the disintegration of the magnetic tablets (mean 90 ± 40 min). Indeed the observed difference could be attributed to the kind of pharmaceutical form, since the powder filled into the capsule was not compressed. It is well known that the compression force is a very important parameter for the tablet manufacturing process, particularly for the development of the time-controlled disintegration (39).

Our findings about disintegration time of magnetic capsules contrasts sharply with those obtained by recent reports (3,4,38). The discrepancy might be due to the pharmaceutical strategies to achieve drug release in the colon (pH-sensitive or enzyme-controlled release), coating thickness and excipients used. Moreover, the criteria adopted for the analysis considered the mean time disintegration started after reaching the ileocolonic region, instead of the complete process.

Magnetic images constitute an innovative approach to characterize the disintegration of pharmaceutical dosage forms in human GI tract (24). The segmentation of the imaging area allowed quantifying the spreading of the magnetic material to characterize the transition between the MM to MT provided by the disintegration process. Although these images presented reasonable quality, the application of restoration techniques could improve image quality and suppress noise simultaneously.

Unfortunately, based on the characteristics of the magnetic formulation, it remains impractical to compare directly our findings with the results obtained from standard imaging techniques. However, great effort has been made to improve the biomagnetic systems and to reduce the amount of ferrite in the magnetic formulation similar to a conventional dosage form. Thereby, this magnetic method could be associated with pharmacokinetic parameters ('magnetopharmacokinetics') to predicting the drug absorption in a specific site of GI tract for optimized pharmacotherapy (40).

In summary, AC Biosusceptometry systems are completely safe and harmless devices, able to evaluate accurately solid dosage forms in human GI tract. Additionally, these systems represent a novel imaging tool to characterize diverse parameters related to drug delivery, thus deserving the same importance as conventional techniques in pharmaceutical research.

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REFERENCES

1. L. Yang, J. S. Chu, and J. A. Fix. Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. *Int. J. Pharm.* **235**:1–15 (2002).
2. M. A. Shareef, R. K. Khar, A. Ahuja, F. J. Ahmad, and S. Raghava. Colonic drug delivery: an updated review. *AAPS Pharm. Sci.* **5**:1–26 (2003).
3. E. T. Cole, R. A. Scott, A. L. Connor, I. R. Wilding, H-U. Petereit, C. Schminke, T. Beckert, and D. Cadé. Enteric coated HPMC capsules designed to achieve intestinal targeting. *Int. J. Pharm.* **231**:83–95 (2002).
4. O. Honkanen, J. Marvola, H. Kanerva, K. Lindevall, M. Lipponen, T. Kekki, A. Ahonen, and M. Marvola. Gamma scintigraphic evaluation of the fate of hydroxypropyl methylcellulose capsules in the human gastrointestinal tract. *Eur. J. Pharm. Sci.* **21**:671–678 (2004).
5. C. S. Leopold. Coated dosage forms for colon-specific drug delivery. *Pharm. Sci. Technol. Today* **2**:197–252 (1999).
6. C. D. Melia and S. S. Davis. Review article: mechanisms of drug release from tablets and capsules. I: disintegration. *Aliment. Pharmacol. Ther.* **3**:223–232 (1989).
7. E. Lipka and G. L. Amidon. Setting bioequivalence requirements for drug development based on preclinical data: optimizing oral drug delivery systems. *J. Control. Release* **62**:41–49 (1999).
8. M. Zahirul and I. Khan. Dissolution testing for sustained or controlled release oral dosage forms and correlation with *in vivo* data: challenges and opportunities. *Int. J. Pharm.* **140**:131–143 (1996).
9. N. Rouge, P. Buri, and E. Doelker. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. *Int. J. Pharm.* **136**:117–139 (1996).

10. M. Singh and V. Waluch. Physics and instrumentation for imaging *in-vivo* drug distribution. *Adv. Drug Deliv. Rev.* **4**:7–20 (2000).
11. I. R. Wilding, A. J. Coupe, and S. S. Davis. The role of γ-scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev.* **46**:103–124 (2001).
12. J. C. Richardson, R. W. Bowtell, K. Mäder, and C. D. Melia. Pharmaceutical applications of magnetic resonance imaging (MRI). *Adv. Drug Deliv. Rev.* **57**:1191–1209 (2005).
13. A. Steingoetter, D. Weishaup, P. Kunz, K. Mäder, H. Lengsfeld, M. Thumshirn, P. Boesiger, M. Fried, and W. Schwizer. Magnetic resonance imaging for the *in vivo* evaluation of gastric-retentive tablets. *Pharm. Res.* **20**:2001–2007 (2003).
14. A. Steingoetter, P. Kunz, D. Weishaupt, K. Mäder, H. Lengsfeld, M. Thumshirn, P. Boesiger, M. Fried, and W. Schwizer. Analysis of the meal-dependent intragastric performance of a gastric-retentive tablet assessed by magnetic resonance imaging. *Aliment. Pharmacol. Ther.* **18**:713–720 (2003).
15. W. Weitschies, O. Kosch, H. Mönnikes, and L. Trahms. Magnetic Marker Monitoring: an application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms. *Adv. Drug Deliv. Rev.* **57**:1210–1222 (2005).
16. J. R. A. Miranda, O. Baffa, and R. B. Oliveira. An AC biosusceptometer to study gastric emptying. *Med. Phys.* **19**:445–448 (1992).
17. L. A. Corá, M. F. Américo, R. B. Oliveira, O. Baffa, R. Moraes, F. G. Romeiro, and J. R. A. Miranda. Disintegration of magnetic tablets in human stomach evaluated by alternate current biosusceptometry. *Eur. J. Pharm. Biopharm.* **56**:413–420 (2003).
18. L. A. Corá, F. G. Romeiro, M. Stelzer, M. F. Américo, R. B. Oliveira, O. Baffa, and J. R. A. Miranda. AC biosusceptometry in the study of drug delivery. *Adv. Drug Deliv. Rev.* **57**:1223–1241 (2005).
19. O. Baffa, R. B. Oliveira, J. R. A. Miranda, and L. E. A. Troncon. Analysis and development of AC biosusceptometer for orocaecal transit time measurements. *Med. Biol. Eng. Comput.* **33**:353–357 (1995).
20. R. B. Oliveira, O. Baffa, L. E. A. Troncon, J. R. A. Miranda, and C. R. Cambrea. Evaluation of a biomagnetic technique for measurement of orocaecal transit time. *Eur. J. Gastroenterol. Hepatol.* **8**:491–495 (1996).
21. J. R. A. Miranda, R. B. Oliveira, P. L. Sousa, F. J. H. Braga, and O. Baffa. A novel biomagnetic method to study gastric antral contractions. *Phys. Med. Biol.* **42**:1791–1799 (1997).
22. R. Moraes, L. A. Corá, M. F. Américo, R. B. Oliveira, O. Baffa, and J. R. A. Miranda. Measurement of gastric contraction activity in dogs by means of AC biosusceptometry. *Physiol. Meas.* **24**:337–345 (2003).
23. M. Moreira, L. Murta, and O. Baffa. Imaging ferromagnetic tracers with an AC biosusceptometer. *Rev. Sci.Instrum.* **71**:2532–2538 (2000).
24. L. A. Corá, U. Andreis, F. G. Romeiro, M. F. Américo, R. B. Oliveira, O. Baffa, and J. R. A. Miranda. Magnetic images of the disintegration process of tablets in the human stomach by ac biosusceptometry. *Phys. Med. Biol.* **50**:5523–5534 (2005).
25. L. A. Corá, F. G. Romeiro, M. F. Américo, R. B. Oliveira, O. Baffa, M. Stelzer, and J. R. A. Miranda. Gastrointestinal transit and disintegration of enteric coated magnetic tablets assessed by ac biosusceptometry. *Eur. J. Pharm. Sci.* **27**:1–8 (2006).
26. E. H. Frei, E. Gunders, M. Pajewsky, W. J. Alkan, and J. Eshcher. Ferrites as contrast material for medical X-ray diagnosis. *J. Appl. Phys.* **39**:99–1001 (1968).
27. V. G. Belikov and A. G. Kuregyan. Generation and medico-biological application of magnetic fields and carriers (review). *Pharm. Chem. J.* **35**:88–95 (2001).
28. A. David, B. Yagen, A. Sintov, and A. Rubinstein. Acrylic polymers for colon-specific drug delivery. *STP Pharma Sci.* **7**:546–554 (1997).
29. K. Lehman. Practical Course in Film Coating of Pharmaceutical Dosage Forms with Eudragit®, Pharma Polymers, Darmstadt, 2001.
30. D. F. Evans, G. Pye, R. Bramley, A. G. Clark, T. J. Dyson, and J. D. Hardcastle Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* **29**:1035–1041 (1988).
31. M. K. Chourasia and S. K. Jain. Pharmaceutical approaches to colon target drug delivery systems. *J. Pharm. Pharmaceut. Sci.* **6**:33–66 (2003).
32. E. M. M. Quigley. Gastric and small motility in health and disease. *Gastroenterol. Clin. North Am.* **25**:113–145 (1996).
33. A. J. Coupe, S. S. Davis, and I. R. Wilding. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. *Pharm. Res.* **8**:360–364 (1991).
34. F. Kedzierewicz, P. Thouvenot, J. Lemut, A. Etienne, M. Hoffman, and P. Maincent. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. *J. Control. Release* **58**:195–205 (1999).
35. S. S. Davis, J. G. Hardy, and J. W. Fara. Transit of pharmaceutical dosage forms through the small intestine. *Gut* **27**:886–892 (1986).
36. D. Harris, J. T. Fell, H. L. Sharma, and D. C. Taylor. GI transit of potential bioadhesive formulations in man: a scintigraphy study. *J. Control. Release* **12**:45–53 (1990).
37. C. J. Kenyon, R. V. Nardi, D. Wong, G. Hooper, I. R. Wilding, and D. R. Friend. Colonic delivery of dexamethasone: a pharmacoscintigraphic evaluation. *Aliment. Pharmacol. Ther.* **11**:205–213 (1997).
38. C. Tuleu, A. W. Basit, W. A. Waddington, P. J. Ell, and J. M. Newton. Colonic delivery of 4-aminosalicylic acid using amylase-ethylcellulose-coated hydroxypropylmethylcellulose capsules. *Aliment. Pharmacol.Ther.* **16**:1771–1779 (2002).
39. K.-H. Lin, S.-Y. Lin, and M.-J. Li. Compression forces and amount of outer coating layer affecting the time-controlled disintegration of the compression-coated tablets prepared by direct compression with micronized ethylcellulose. *J. Pharm. Sci.* **90**:2005–2009 (2001).
40. H. Zhou. Pharmacokinetic strategies in deciphering atypical drug absorption profiles. *J. Clin. Pharmacol.* **43**:211–227 (2003).